

REMARKS

Claims 1, 2, 8, and 11-21 are pending in the application. The claims have not been amended by the present response. The specification has been amended to insert sequence identifiers and amend selected figure descriptions. No new matter has been added.

Drawings

Several of the drawings were objected to on the Form PTO-948 enclosed with the Office Action. Replacement drawings are enclosed with the present response. Figures 1, 4, 5, and 16 have been amended to revise the figure numbering and lettering. These amendments add no new matter.

Information Disclosure Statement

At page 2 of the Office Action, the Examiner stated that the Information Disclosure Statement filed on May 27, 2005 has been entered into the record, but that Reference ANN contained insufficient identifying information and was not considered. The Information Disclosure Statement enclosed with the present response contains full identifying information for Reference ANN (GenBank Accession AA844072).

Objections to the Specification

The Brief Description of the Drawings was objected to with respect to the descriptions of Figures 1, 4, and 5. The descriptions for these figures have been amended to overcome the present objection.

The Office Action stated that sequence identifiers must be used for the sequences appearing in Figure 8. The Brief Description of the Drawings has been amended to provide sequence identifiers for the several sequences depicted in Figure 8. The enclosed substitute sequence listing contains the sequences contained in the figure (SEQ ID NOS:58-63). Further,

paragraphs [0051] and [0052] have been amended to provide sequence identifiers for the sequences depicted in Figures 14 and 15 (SEQ ID NOS:52-57).

The Office Action stated that “[s]equences appear in Tables 3 and 5, of the specification but are not identified by SEQ ID NO as required.”

Table 3 (page 59) is an amino acid sequence comparison of neublastin to persephin, neurturin, and GDNF. Paragraph [0268] immediately precedes Table 3 and provides sequence identifiers for the sequences presented in the table. Table 3 has been amended to incorporate the sequence identifiers referenced in paragraph [0268]. In addition, Table 3 has been amended to include sequence identifiers for those sequences in the bottom portion of the table that contain four or more amino acid residues. The sequences are included in the enclosed substitute Sequence Listing as SEQ ID NOS:64-75.

Table 5 (pages 81-82) is an alignment of neublastin polypeptides. Table 5 provides (in the left margin) sequence identifiers (SEQ ID NOS:2, 4, and 9) for each of the three neublastin polypeptides depicted in the table. Furthermore, the sequences depicted in Table 5 are also described (with SEQ ID NOS) in paragraph [0353], which immediately precedes Table 5 on page 81.

In view of the foregoing, applicants respectfully submit that all of the sequences depicted in Tables 3 and 5 are properly identified with SEQ ID NOS and that no further amendments are required.

Paragraph [0270] has been amended to insert a sequence identifier. The sequence in paragraph [0270] is now SEQ ID NO:76 in the substitute Sequence Listing filed herewith.

The paper and computer-readable copy of the Sequence Listing filed herewith are the same and contain no new matter. Applicants submit that the amendments to the specification fulfill the requirements under 37 C.F.R. §§1.821-1.825.

35 U.S.C. §101 (Utility) and 35 U.S.C. §112, First Paragraph (Enablement)

At page 3 of the Office Action, claims 1, 2, 8, and 11-21 were rejected as allegedly not supported by a specific, substantial, and credible asserted utility or a well established utility. In a related rejection at page 4 of the Office Action, the claims were rejected as allegedly not enabled.

Applicants respectfully traverse the rejection in view of the following remarks.

The present application describes the identification and characterization of a neurotrophic factor termed "neublastin." Neublastin was determined to be a member of the GDNF ligand subfamily of neurotrophic factors and was shown to exhibit neurotrophic activity. All members of the GDNF ligand subfamily (GDNF, neurturin, persephin, and Neublastin) signal through the RET receptor tyrosine kinase but differ in their affinities for a family of neurotrophic RET co-receptors, the GFR α receptors. Unlike other GDNF ligands (which preferentially bind to a complex containing RET and GFR α 1, GFR α 2, or GFR α 4), Neublastin exhibits high affinity for the GFR α 3-RET receptor complex.

Human pre-pro Neublastin (SEQ ID NO:9) is 220 amino acids in length. The amino acid residues of SEQ ID NO:9 are numbered such that residues 780 through 71 correspond to the pre-pro section of the Neublastin polypeptide and residues 1 to 140 correspond to a predicted mature polypeptide (see specification at paragraph [0007]). Independent claim 1 is directed to a polypeptide consisting of an amino acid sequence selected from the group consisting of: (a) amino acids 37-140 of SEQ ID NO:9 (NBN 104; also designated SEQ ID NO:43 in paragraph [0072]); (b) amino acids 39-140 of SEQ ID NO:9 (NBN 102; also designated SEQ ID NO:45 in paragraph [0074]); and (c) amino acids 42-140 of SEQ ID NO:9 (NBN 99; also designated SEQ ID NO:48 in paragraph [0077]).

The Office Action stated that the claims

are directed to a polypeptide comprising SEQ ID NO:2. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

Contrary to the passage reproduced above from the Office Action, no claim pending in the present application recites SEQ ID NO:2. The following remarks are premised on the assumption that the rejection was intended to apply to the claimed polypeptides.

The application as filed contained the following experimental findings that demonstrate the neurotrophic activity of neublastin: neublastin promotes survival of rat embryonic dopaminergic neurons (Example 6); neublastin promotes survival of porcine embryonic dopaminergic neurons (Example 7); and neublastin promotes survival of murine dorsal root ganglion cells (at a level that is comparable to or better than the neurotrophic factors GDNF and neurturin; Example 8). The mature form of human neublastin encoded by the nucleotide sequence of SEQ ID NO:8 was used in the foregoing examples.

Examples 11 and 12 describe the preparation and analysis of truncates of neublastin. Example 11 describes a 102 amino acid form (NBN102) and Example 12 describes a 99 amino acid form (NBN99) and a 104 amino acid form (NBN104) of truncated rat neublastin. These truncates were found to exhibit biological activity (as measured by their ability to induce RET autophosphorylation) that was at least equivalent to that of the 113 amino acid form of mature, rat neublastin.

The Office Action stated that

Applicants disclose in the specification that the claimed receptor is believed to be a Neublastin which exhibits high affinity for GFPa3-RET (page 2 of the specification). Applicants also provide numerous examples in the specification regarding Neublastin.... However, it is not clear, first what the specific substantial utility is of the protein of the present invention with respect to its ability to bind to GFPa3-RET. Second, it is not clear if the Examples discussed above are art-accepted models and, third, it is not clear if the claimed protein is, in fact, the protein used in the Examples.

The three items mentioned in the passage reproduced above are addressed in the order that they were raised.

First, neublastin binds to a complex containing the membrane-bound RET receptor tyrosine kinase and the GFR α 3 co-receptor. The formation of a neublastin-RET-GFR α 3 ternary complex triggers a signal transduction pathway that ultimately results in neublastin-induced

neurotrophic activity (which activity constitutes a specific and substantial utility). RET autophosphorylation is an event that occurs early in this signal transduction pathway, subsequent to neublastin binding to RET and GFR α 3. Assays that detect a neublastin polypeptide forming a ternary complex with RET and GFR α 3 and/or triggering RET autophosphorylation are convenient means for measuring the bioactivity of a neublastin polypeptide (see, e.g., Examples 5, 11, and 12).

Second, the application's experimental findings demonstrate the ability of neublastin to promote the survival of neurons and thus confirm the neurotrophic activity of the protein (see Examples 6-8, summarized above). The extensive experimental findings contained in the application as filed confirm neublastin's utility as a neurotrophic factor.

Third, Examples 6-8 were performed using a mature human neublastin and demonstrate cross-species reactivity of the protein (human neublastin was found to promote survival of rat, porcine, and murine cells). Examples 11 and 12 were performed using truncates of rat neublastin that are 104, 102, and 99 amino acids in length (these truncates are termed, respectively, "NBN104," "NBN102," and "NBN99"). Examples 11 and 12 demonstrate that NBN104, NBN102, and NBN99 possess bioactivity (as measured in RET autophosphorylation assays) that is comparable to that of wild type neublastin.

The claimed polypeptides are the human counterparts of the rat neublastin truncates (NBN104, NBN102, and NBN99) characterized in Examples 11 and 12. In view of the specification's demonstration of bioactivity for the rat truncates NBN104, NBN102, and NBN99, the person of ordinary skill in the art would understand that that corresponding human truncates recited in claim 1 form a ternary complex with RET and GFR α 3, trigger RET autophosphorylation, and induce neurotrophic activity. The neurotrophic activity of the claimed polypeptides (and pharmaceutical compositions containing same) constitutes a specific, substantial, and credible utility.

In view of the foregoing, applicants respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

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CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-056001.

Respectfully submitted,

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